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# Anaphylaxis during surgical and interventional procedures

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**Objective:** To describe the current evidence-based knowledge of the causes, diagnostic evaluation, and treatment of patients with anaphylaxis associated with surgical and interventional procedures.

**Data Sources:** Articles published between 1966 and 2003 were identified in MEDLINE using the keywords *anaphylactoid*, *anaphylaxis*, *anesthetics*, *antibiotics*, *cephalosporins*, *contrast media*, *colloids*, *flow cytometry*, *hypersensitivity*, *latex*, *neuromuscular depolarizing agents*, *neuromuscular nondepolarizing agents*, *penicillins*, *radioallergosorbent test*, *skin test*, and *vancomycin*. Additional studies were identified from article reference lists.

**Study Selection:** Relevant, peer-reviewed original research articles and reviews.

**Results:** Neuromuscular blocking agents, natural rubber latex, antibiotics, and induction agents are the most common causes of anaphylaxis during surgical and interventional procedures. Colloids, opioids, and radiocontrast media probably account for less than 10% of all reactions. Newer agents implicated in anaphylaxis include isosulphan blue and chlorhexidine. Skin tests are useful for evaluating allergic reactions to anesthetic agents and penicillins and for selecting alternative agents. Skin testing and specific IgE measurements for latex vary in allergen standardization and sensitivity and specificity, respectively. Flow cytometric allergen stimulation tests show promise in differentiating allergic from idiosyncratic ("pseudoallergic") reactions. Drug desensitization has been shown to be useful for penicillin anaphylaxis. Premedication with histamine receptor antagonists and corticosteroids helps prevent or attenuate radiocontrast media reactions.

**Conclusions:** Anaphylaxis during surgical and interventional procedures may be difficult to evaluate because of the rapid, successive use of multiple drugs or diagnostic agents. Careful analysis of anesthetic records and diagnostic tests for all the putative agents are necessary to ensure a complete evaluation.

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## INTRODUCTION

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. The European Academy of Allergology and Clinical Immunology<sup>1</sup> position paper suggests that anaphylactic-type reactions should be reclassified as allergic or nonallergic anaphylaxis. Allergic anaphylaxis is further classified as IgE- or non-IgE-mediated reactions.<sup>1</sup> However, this nomenclature has not been adopted worldwide. The terms *anaphylactoid* and *anaphylactic* remain commonly used in differentiating non-IgE-mediated (including other immunologically mediated mechanisms) and IgE-mediated reactions, respectively.<sup>2</sup> Hypotension and severe bronchospasm do not have to be present for a reaction to be classified as anaphylaxis. The incidence of anaphylaxis during general anesthesia (GA) varies from 1:10,000 to 1:20,000 in an Australian series<sup>3</sup> and is 1:13,000 in a French series,<sup>4</sup> and mortality is 3.4%<sup>5</sup> to 6%.<sup>4</sup> There have not been any large epidemiologic studies from the United States. The most frequent causes of anaphylaxis during surgical and medical procedures are neuromuscular blocking agents (NMBAs), natural rubber latex (NRL), antibiotics, and induction agents.<sup>6</sup>

Colloids, opioids, and radiocontrast media (RCM) probably account for less than 10% of all reactions.<sup>5,7</sup>

Anaphylaxis during surgical and interventional procedures may be difficult to evaluate in view of the many drugs, infusion products, and diagnostic agents that are given, often in quick succession, during the immediate preoperative, intraoperative, and postoperative periods. Although a detailed examination of the anesthetic record and verification of the events with the attending anesthetist are imperative, making an accurate diagnosis of the putative agent can be difficult based on clinical history alone. Table 1 summarizes the variety of putative agents administered during each stage of the operative period.

### Diagnostic Tests

Although different diagnostic tests, including serum tryptase, plasma histamine, specific IgE level measurements, and skin tests, exist for the various agents, these tests are not without their pitfalls. An elevated serum tryptase level 1 to 6 hours after a suspected anaphylactic reaction indicates mast cell degranulation and supports a diagnosis of anaphylaxis in the presence of a suggestive history and clinical findings.<sup>8</sup> However, it will not differentiate IgE- and non-IgE-mediated anaphylaxis.<sup>9</sup> There are several forms of tryptase. Although anaphylaxis is characterized by elevations in  $\beta$ -tryptase levels, commercial assays measure total tryptase. Serum tryptase concentration may, however, be normal even in fatal anaphylaxis.

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Table 1. Agents with the Potential for Anaphylaxis during Surgical and Interventional Procedures

| Preoperative                        | Intraoperative (LA/RA)       | Intraoperative (GA)                 | Immediate postoperative     |
|-------------------------------------|------------------------------|-------------------------------------|-----------------------------|
| Preoperative antibiotics            | LAs                          | Neuromuscular blocking agents*      | Opioids                     |
| Penicillins                         | p-Aminobenzoic acid esters   | Quarternary ammonium compounds      | NSAIDs                      |
| Cephalosporins                      | Benzocaine                   | Succinylcholine                     | Neostigmine                 |
| Vancomycin                          | Butacaine (Butyn)            | Benzylisoquinolinones               | Atropine/<br>Glycopyrrolate |
|                                     | Butethamine (Monocaine)      | Atracurium                          |                             |
| Opioids                             | Chlorprocaine (Nesacaine)    | Mivacurium                          |                             |
| Benzodiazepines                     | Procaine (Novocain)          | Doxacurium                          |                             |
| Natural rubber latex                | Tetracaine (Pontocaine)      | Cisatracurium                       |                             |
| Chlorhexidine                       |                              | Aminosteroids                       |                             |
|                                     | Benzoic acid esters lacking  | Pancuronium                         |                             |
| Blood and colloid infusion products | p-aminobenzoyl group         | Vecuronium                          |                             |
| Haemaccel                           | Amydracaine (Alypin)         | Rocuronium                          |                             |
| Gelafundin                          | Cyclomethycaine (Surfacaine) | Rapacuronium                        |                             |
|                                     | Isobucaine (Kincaine)        | Hypnotics*                          |                             |
|                                     | Mepylcaine (Oracaine)        | Thiopentone                         |                             |
|                                     | Metabutethamine (Oracaine)   | Propofol                            |                             |
|                                     | Piperocaine (Metycaine)      | Etomidate                           |                             |
|                                     | Proparacaine (Ophthaine)     | Opioids*                            |                             |
|                                     |                              | Fentanyl                            |                             |
|                                     | Amide                        | Sufentanil                          |                             |
|                                     | Bupivacaine (Marcaine)       | Pethidine                           |                             |
|                                     | Dibucaine (Nupercaine)       | Neuroleptics*                       |                             |
|                                     | Dyclonine (Dyclone)          | Benzodiazepines*                    |                             |
|                                     | Diperoxon (Diothane)         | Midazolam                           |                             |
|                                     | Lidocaine (Xylocaine)        | Diazepam                            |                             |
|                                     | Mepivacaine (Carbvocaine)    | LAs†                                |                             |
|                                     | Oxethazaine (Oxaine)         | Others                              |                             |
|                                     | Phenacaine (Holocaine)       | Isosulphan blue                     |                             |
|                                     | Pramoxine (Tronothane)       | Radiocontrast media                 |                             |
|                                     | Prilocaine (Citonest)        | Aprotinin                           |                             |
|                                     |                              | Natural rubber latex                |                             |
|                                     | Natural rubber latex         | Chlorhexidine                       |                             |
|                                     | Opioids†                     | Blood and colloid infusion products |                             |
|                                     | Benzodiazepines†             | Haemaccel                           |                             |
|                                     | Propofol†                    | Gelafundin                          |                             |

Abbreviations: GA, general anesthesia; LA, local anesthesia; NSAIDs, nonsteroidal anti-inflammatory drugs; RA, regional anesthesia.

\* Used during induction and maintenance of GA.

† Opioids, benzodiazepines, and propofol may be used for sedation and adjuvant analgesia during procedures performed with the patient under LA or RA. Similarly, LAs may be used for tissue infiltration in procedures performed with the patient under GA.

Plasma histamine levels peak at 15 to 30 minutes and return to baseline values within 1 hour of the onset of anaphylaxis. Although of limited use, measurement of plasma histamine concentration within minutes of a possible anaphylactic reaction may be helpful diagnostically in some patients.<sup>10,11</sup>

In this review, we evaluate the evidence for our current understanding of the causes, diagnostic evaluation, and treatment of patients with anaphylaxis associated with surgical and interventional procedures. Relevant, peer-reviewed original research articles and reviews published between 1966 and 2003 were identified in MEDLINE using the keywords *anaphylactoid, anaphylaxis, anesthetics, antibiotics, cephalosporins, contrast media, colloids, flow cytometry, hypersensitivity, latex, neuromuscular depolarizing agents, neuromuscular nondepolarizing agents, penicillins, radioallergosorbent test, skin test,*

and *vancomycin*. Additional studies were identified from article reference lists.

#### GA Agents and NMBAs

Tables 1 and 2 summarize the various drugs used during the induction, maintenance, and reversal of GA. The NMBAs are classified as depolarizing (prototype: succinylcholine) or nondepolarizing blocking drugs. The 2 major families of nondepolarizing blocking drugs comprise isoquinoline derivatives (Fig 1) and steroids (Fig 2). The main agents used for induction of anesthesia are hypnotics (thiopentone, propofol, and etomidate), opioids (fentanyl), neuroleptics, and benzodiazepines. The NMBAs, commonly used to induce paralysis to facilitate endotracheal intubation or to optimize surgical exposure, account for most cases of intraoperative anaphy-

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\* Suitable for rapid sequence induction.



laxis.<sup>12</sup> Although rocuronium and succinylcholine were the most frequently incriminated NMBA's in a recent French study,<sup>13</sup> the frequencies of the putative drugs vary according to the relative amounts of each NMBA used in each country.<sup>4</sup> Recently, anaphylaxis from newer NMBA's, such as rapacuronium, mivacurium, and cisatracurium, has also been reported.<sup>14</sup>

The use of intradermal skin tests (IDTs) for the diagnosis of IgE-mediated anaphylaxis to agents used during GA is well established.<sup>15-18</sup> Some authors<sup>17,19,20</sup> have reported the usefulness of skin prick tests (SPTs). In the United Kingdom, an SPT wheal measuring 2 mm or more larger than the negative control to 1:10 dilution of the anesthetic agent is considered to be a true-positive reaction.<sup>21</sup> The additional utility in performing SPT is that of avoiding potentially dangerous reactions by doing intradermal testing without prick testing. However, SPTs have not been shown to be useful for certain drugs, such as propofol, in view of poor sensitivity.

Various authors have used different dilutions and concentrations of NMBA's, hypnotics, and induction agents for skin testing (Table 3). Based on these studies, SPT using 1:10 dilution followed by 1:1 dilution and IDT starting at 1:1,000 dilution seems to be a sensible clinical approach. Cross-sensitivity between NMBA's occurs in up to 60% of patients in studies based on NMBA-specific IgE levels measured by radioimmunoassay and intradermal tests.<sup>22-24</sup> Skin testing is useful in that should an NMBA be incriminated by skin testing, an alternative NMBA producing a negative skin test reaction may be used safely,<sup>24</sup> bearing in mind that the true-negative predictive value for these skin tests is unknown and that false-negative skin test reactions have been reported.<sup>25</sup> Other issues contributing to the variability of skin test results include positive wheal and flare responses independent of mast cell degranulation (atracurium and rocuronium), differing threshold concentrations of test reagents in diagnosis.

Table 3. Suggested Concentrations for Drug Skin Tests

| Medication      | Concentration (mg/mL)               |                             |                                     |                                       |                                       |                                     |                                  |                                        |
|-----------------|-------------------------------------|-----------------------------|-------------------------------------|---------------------------------------|---------------------------------------|-------------------------------------|----------------------------------|----------------------------------------|
|                 | Intradermal skin test               |                             |                                     |                                       |                                       | Skin prick test                     |                                  |                                        |
|                 | Vervloet et al <sup>15</sup> (1983) | Fisher <sup>16</sup> (1984) | Moscicki et al <sup>17</sup> (1990) | Fisher and Bowey <sup>19</sup> (1997) | Rose and Fisher <sup>18*</sup> (2001) | Moscicki et al <sup>17</sup> (1990) | Pepys et al <sup>20</sup> (1994) | Fisher and Bowey <sup>19*</sup> (1997) |
| Succinylcholine | 0.1                                 | 0.05                        | 0.02                                | 0.05/0.10                             | 0.05                                  | 0.2                                 | 50                               | 50                                     |
| Pancuronium     | 0.2                                 | 0.002                       | 0.002                               | 0.004/0.008                           | 0.002                                 | 0.02                                | 2                                | 2                                      |
| Vecuronium      | 0.4                                 | —                           | —                                   | 0.004/0.008                           | 0.004                                 | —                                   | —                                | 4                                      |
| Alcuronium      | 0.05                                | 0.005                       | —                                   | 0.005/0.01                            | 0.005                                 | —                                   | 5                                | 5                                      |
| Tubocurarine    | 0.003                               | 0.001                       | 0.0003                              | 0.001/0.01                            | 0.001                                 | 0.003                               | 10                               | 10                                     |
| Gallamine       | 0.2                                 | 0.04                        | —                                   | 0.04/0.08                             | 0.04                                  | —                                   | 40                               | 40                                     |
| Metocurine      | —                                   | —                           | 0.002                               | —                                     | —                                     | 0.02                                | —                                | —                                      |
| Methohexital    | —                                   | 0.1                         | 0.1                                 | 0.1                                   | —                                     | 1.0                                 | —                                | 10                                     |
| Protamine       | —                                   | 0.001                       | —                                   | 0.05                                  | —                                     | —                                   | —                                | 50                                     |
| Thiopental      | —                                   | 0.25                        | 0.20                                | 0.25                                  | —                                     | 2.0                                 | 50                               | 25                                     |
| Thiamylal       | —                                   | —                           | 0.01                                | —                                     | —                                     | 1.0                                 | —                                | —                                      |
| Rocuronium      | 0.1                                 | —                           | —                                   | —                                     | 0.01                                  | —                                   | —                                | —                                      |
| Mivacurium      | 0.002                               | —                           | —                                   | —                                     | 0.002                                 | —                                   | —                                | —                                      |
| Atracurium      | —                                   | —                           | —                                   | —                                     | 0.001                                 | —                                   | 10                               | —                                      |
| Cisatracurium   | —                                   | —                           | —                                   | —                                     | 0.002                                 | —                                   | —                                | —                                      |
| Decamethonium   | —                                   | —                           | —                                   | —                                     | 0.002                                 | —                                   | —                                | —                                      |
| Codeine         | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | 60                               | —                                      |
| Morphine        | —                                   | —                           | —                                   | 0.0001                                | —                                     | —                                   | —                                | 1                                      |
| Pethidine       | —                                   | —                           | —                                   | 0.0005                                | —                                     | —                                   | —                                | 5                                      |
| Papaveretum     | —                                   | —                           | —                                   | 0.0002                                | —                                     | —                                   | —                                | 2                                      |
| Diazepam        | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | —                                | 5                                      |
| Midazolam       | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | —                                | 5                                      |
| Neostigmine     | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | —                                | 2.5                                    |
| Atropine        | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | —                                | 0.6                                    |
| Benzylkonium    | —                                   | —                           | —                                   | 0.05                                  | —                                     | —                                   | 100                              | —                                      |
| Droperidol      | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | 5                                | 5                                      |
| Fentanyl        | —                                   | —                           | —                                   | 0.001                                 | —                                     | —                                   | 0.05                             | 0.1                                    |
| Alfentanil      | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | 0.5                              | —                                      |
| Propofol        | —                                   | —                           | —                                   | 0.06                                  | —                                     | —                                   | 10                               | 10                                     |
| Dextran 70      | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | 50                               | 6                                      |
| Gelofusine      | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | 40                               | —                                      |
| Haemaccel       | —                                   | —                           | —                                   | —                                     | —                                     | —                                   | 35                               | 3.5                                    |

\* Positive intradermal skin test result: wheal greater than 8 mm; positive skin prick test result: wheal greater than 4 mm.

ing a positive skin test result, variable antigenicity of NMBA, and sites chosen for skin testing (the volar aspect of the forearm vs the upper back).<sup>26</sup>

Drug-specific IgE has been demonstrated by radioimmunoassay and radioallergosorbent testing (RAST) by some authors.<sup>23,27-29</sup> However, only the RAST or CAP System fluorescein enzyme immunoassay (FEIA; Pharmacia, Uppsala, Sweden), a sensitive, quantitative, capsulated hydrophilic carrier polymer method, for suxamethonium is currently commercially available.

Flow cytometry is a technique for the analysis of physical and biological characteristics of cells or other biological particles when labeled with antibodies coupled to fluorochromes or other dyes. The basophil activation test, also called the flow cytometric allergen stimulation test (FAST) via detection of CD63 expression (commercially available under the name Flow-CAST [Buhlmann Laboratories, Allschwil, Switzerland] or BASOTEST [Becton-Dickinson, Franklin Lakes, NJ]), is based on the in vitro allergen-induced specific activation of basophils. Flow cytometry is a reliable method for the quantification of basophil activation after allergenic stimulus in vitro and in vivo. It also enables detection of allergic and pseudoallergic reactions by mechanisms other than allergen-specific IgE antibodies. The FAST has been shown to have good specificity but low sensitivity when used to test for NMBA allergy to suxamethonium, gallamine, vecuronium, and pancuronium, correlating strongly with skin test results.<sup>30</sup> Although the FAST is an emerging diagnostic tool, it is not currently available commercially.

Patients who have had a previous reaction to an agent used during GA should have IDT done to both the putative and an alternative NMBA. Low-risk NMBA (benzylisoquinolines followed by aminosteroids), such as pancuronium, should be used in preference to high-risk agents, such as succinylcholine, if both have skin test negative results. The anesthesiologist and patient need to be aware that a negative skin test

result does not eliminate the chance of developing a reaction to that NMBA.

Although rapid intravenous desensitization has been described in case reports, pretreatment for NMBA allergy has been found to be totally ineffective.<sup>31</sup> This is in contrast to effective premedication protocols available for prophylaxis against RCM reactions, which are discussed later herein. Desensitization has a very limited role in clinical practice and is rarely required because one can almost always find a suitable alternative drug.

#### Local Anesthetic Agents

Although adverse reactions to local anesthetic (LA) agents are not uncommon, true allergic reactions compose less than 1% of these reactions.<sup>32</sup> The most common adverse reactions are vasovagal reactions, which are also the most common presenting complaints in referrals to allergists for evaluation of potential allergy to LA agents. Although some of these adverse reactions may be due to the preservatives (parabens, sodium metabisulphite, and parahydroxybenzoic acid ester), these have often not been consistently reproduced on challenge. Local anesthetic agents are classified as benzoic acid esters or amide derivatives (Table 1). Cross-reactivity among LA agents has been reported based on the results of patch testing. Benzoic acid esters often cross-react with each other but do not cross-react with amide derivatives. Although cross-reactivity among amide LA agents has been poorly studied, they are probably not substantially cross-reactive with one another.

Several groups have proposed diagnostic protocols using SPT and IDT followed by challenge tests where appropriate to both the LA agent and the preservative. An example of such a protocol is given in Table 4. Positive skin test reactions may occur in approximately 15% of patients with no history of adverse reactions to LA agents. False-positive skin test reactions confirmed by a subsequent negative challenge

Table 4. Example of a Diagnostic Protocol for Local Anesthetics\*

| Reagents                                          | Step | Route | Volume  | Dilution  |
|---------------------------------------------------|------|-------|---------|-----------|
| Skin test†                                        |      |       |         |           |
| LA agent (1%) (SPT and IDT)                       | 1    | SPT   | —       | 1:100     |
| Preservative (SPT only)                           | 2    | SPT   | —       | Undiluted |
| Parahydroxybenzoic acid ester 1%                  | 3    | IDT   | 0.02 mL | 1:100     |
| Sodium metabisulphite 5%                          |      |       |         |           |
| Subcutaneous incremental challenge‡               |      |       |         |           |
| LA agent (1%, SC cumulative dose to 3.8 mL)       | 1    | SC    | 0.1     | 1:100     |
| Preservatives                                     | 2    | SC    | 0.1     | 1:10      |
| Parahydroxybenzoic acid ester, 20 mg PO           | 3    | SC    | 0.1     | Undiluted |
| Sodium metabisulphite, 10 mg PO                   | 4    | SC    | 0.5     | Undiluted |
| Methyl-4-hydroxybenzoate, 4 mg/mL and 20 mg/mL SC | 5    | SC    | 1.0     | Undiluted |
| Sodium metabisulphite, 2 mg/mL and 10 mg/mL       |      |       |         |           |

Abbreviations: IDT, intradermal test; LA, local anesthetic; PO, by mouth; SC, subcutaneous; SPT, skin prick test.

\* Adapted from Schatz<sup>33</sup> and Gall et al. (*J Allergy Clin Immunol.* 1996;97:933-937).

† Administer skin test steps at 20-minute intervals.

‡ Administer SC incremental challenge steps at 20- to 30-minute intervals.

occur in up to 9% of patients studied. False-negative skin test reactions have also been reported in the literature. Thus, incremental challenge is the preferred method of diagnosis of hypersensitivity to LA agents.<sup>33</sup> Although measurement of LA-specific IgE levels is available in certain specialized laboratories, it has not been standardized and is not commercially available.

A patient is thus diagnosed as having allergy to the specific LA agent in the presence of a consistent history and positive skin test reactions. A positive subcutaneous incremental challenge need not be demonstrated, except where there are no effective alternatives available (eg, lidocaine for cardiac arrhythmia). Skin testing to a potentially non-cross-reacting LA agent should be carried out, followed by a subcutaneous incremental challenge if the skin test reaction is negative. The patient should then be given a note on the specific LA agent tolerated, its preservative content, the final dose given, and the absence of increased risk over the general population of an immunologic reaction to subsequent administration of the LA agent.

#### *Natural Rubber Latex*

Patients at risk of anaphylaxis to NRL include those who require long-term bladder care, those who have undergone multiple surgical procedures, health care workers, and atopic individuals. The most frequent types of surgical procedures during which NRL anaphylaxis occurs are obstetric and gynecologic, abdominal, and orthopedic surgical procedures. Reactions to NRL usually occur during maintenance anesthesia, in contrast to reactions from NMBA, opioids, and sedatives, which usually occur during induction.<sup>34</sup>

However, there are several issues regarding the use of SPT and in vitro latex-specific IgE assays in the diagnosis of NRL allergy.<sup>35</sup> The sensitivities and specificities of SPT vary with NRL source materials (nonammoniated latex [NAL], ammoniated latex, and glove extracts) and whether they were compared with the clinical history of the patient or outcomes of a 2-stage glove provocation test. To date, SPTs using Greer (Greer Laboratories, Lenoir, NC) and Stallergenes (Stallergenes, Fresnes, France) NAL extracts seem to be most comparable. The former is pending approval from the Food and Drug Administration in the United States, and the latter is approved for use in Europe. The overall sensitivity of Greer's NAL extract based on a multicenter phase 3 clinical study<sup>36</sup> of 324 subjects was 70% to 75% based on clinical history and 95% based on glove provocation challenge. The specificity was 97% to 99% based on clinical history or glove provocation challenge. The diagnostic sensitivity of Stallergenes NAL SPT reagent was 93% and specificity was 100% based on clinical history in 46 latex allergic and 76 non-latex allergic patients.

Three established Food and Drug Administration–approved in vitro latex-specific IgE assays are available: the Pharmacia CAP system (Pharmacia, Peapack, NJ), the DPC Microplate Alastat assay (Diagnostic Products Corp, Los Angeles, CA), and the HyTECH assay (Hycor Biomedical

Inc, Garden Grove, CA). Both the Pharmacia CAP and DPC Microplate Alastat assays showed comparable sensitivity of 73% to 76% and specificity of 97%. The HyTECH assay had a much lower specificity of 73%.<sup>37</sup> In addition, receiver operating characteristic curve analyses have demonstrated that the manufacturer-designated positive cutoff value of less than 0.35 kIU/L produced optimal performance in the Pharmacia CAP and DPC Microplate Alastat assays.<sup>38</sup> Although in vivo provocation tests, such as a 2-stage glove provocation test, may be helpful in cases of discordance between convincing NRL-associated symptoms and repeatedly negative SPT reactions or latex-specific IgE measurements, they are usually performed in research settings and not in routine clinical practice.<sup>39</sup>

The FAST has been found to be a highly reliable technique (93% sensitivity and 100% specificity) in the in vitro diagnosis of IgE-mediated latex allergy with good correlation with latex-specific IgE measurements.<sup>40</sup> Using anti-CD203 instead of anti-CD63 as a marker of basophil activation has been shown to improve the sensitivity of the assay.<sup>41</sup>

#### *Preoperative Antibiotics*

The common prophylactic antibiotics given preoperatively are penicillins, cephalosporins (cefotaxime, cephalothin, and cefazolin), gentamicin, and vancomycin, the latter for patients at risk of methicillin-resistant *Staphylococcus aureus* infections. The most reliable method for evaluating suspected anaphylaxis to penicillin is skin testing to the major and minor determinants of penicillin. If penicilloyl polylysine (the major determinant) and penicillin G are used for skin testing, 97% of patients with a negative skin test reaction will tolerate penicillin administration. If the skin test reaction to both the major and minor determinants (which is not commercially available) is negative, 97% to 99% of patients will tolerate penicillin administration at the time of testing without risk of an immediate reaction. Thus, the skin test has a high negative predictive value. In the presence of a positive history and positive skin test reactions, there is a greater than 50% chance of an immediate reaction if penicillin is given.<sup>42</sup> Alternatively, positive drug-specific IgE test results using RAST or CAP FEIA may suggest a diagnosis of penicillin allergy. However, negative test results are unreliable because they are insensitive. Thus, skin tests are preferred.

Patients with a history of penicillin anaphylaxis and positive skin test reactions should not receive penicillin. However, if an alternative antibiotic is not available, penicillin desensitization, orally or parenterally, according to an established protocol may be undertaken.<sup>43–45</sup>

The cross-hypersensitivity between penicillins and cephalosporins pertain primarily to immediate-type hypersensitivity reactions and in particular to first- and second-generation cephalosporins. This is less than 5% to 10%. Skin testing with cephalosporins (3 mg/mL) is not standardized, and, hence, the negative predictive value is unknown. Skin testing with cefotaxime (SPT: 50 mg/mL; IDT: 0.05 mg/mL) and cephalothin (SPT: 100 mg/mL; IDT: 1 mg/mL) has been used in

the evaluation of intraoperative anaphylaxis.<sup>19</sup> Thus, patients with a definite history suggestive of IgE-mediated hypersensitivity to penicillin and who require a cephalosporin in the absence of suitable non- $\beta$ -lactam alternatives should have skin tests to penicillin performed before receiving a cephalosporin. If the skin test reaction is negative, there is still a possibility of an allergic reaction that is side chain dependent and not dependent on the  $\beta$ -lactam ring shared by the cephalosporin and penicillin molecules.<sup>46</sup> If the skin test reaction is positive, cephalosporin desensitization may be considered. Protocols for desensitization to ceftazidime<sup>47</sup> and cefotaxime<sup>48</sup> have been described elsewhere.

Vancomycin hypersensitivity commonly occurs in the form of red man syndrome from direct mast cell histamine release. Diagnosis is made from clinical history. In red man syndrome that does not respond to a slower rate of infusion, pretreatment with antihistamine or a slow incremental infusion regimen similar to desensitization may be considered.<sup>49,50</sup>

### *Opioids*

Opioids are commonly used perioperatively for analgesia, for sedation, and as adjuvants to inhalational or intravenous anesthetics. Morphine, codeine, and synthetic opioids such as pethidine can cause direct mast cell degranulation without the presence of specific IgE antibodies. Only one possible case of an IgE-mediated reaction to papaveretum<sup>51</sup> and 3 other possible cases of sensitivity to pethidine, morphine, and fentanyl<sup>3,52</sup> have been described in the literature. The SPT has not been found to be helpful in the diagnosis of opioid sensitivity, and direct placebo-controlled challenges may be required to make the diagnosis.<sup>53</sup>

### *Nonsteroidal Anti-inflammatory Drugs*

Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause anaphylactic or anaphylactoid reactions when given in the perioperative period for analgesia. Anaphylaxis to NSAIDs is typically drug specific, in contrast to respiratory-induced reactions. Because most NSAID reactions are not IgE mediated, FAST assays are being developed to differentiate allergic and idiosyncratic reactions to NSAIDs.<sup>54</sup>

### *Radiocontrast Media*

The RCM are used in many interventional procedures, including coronary and cerebral angiography and intraoperative cholangiography. The diagnosis of RCM-associated nonallergic anaphylaxis is based on clinical history alone. Because the cause in most cases is idiosyncratic, there is no role for skin tests or the measurement of specific IgE levels. A history of previous moderate or severe generalized reaction to RCM, cardiovascular disorders, atopy, and asthma are important risk factors for RCM-associated anaphylaxis.<sup>55</sup> In very high-risk patients, intravascular RCM administration should be avoided if possible. If the examination is considered essential, nonionic RCM are the agents of choice.

The most widely used pretreatment regimen for patients with a previous immediate RCM reaction consists of the use of low-osmolality RCM, 50 mg of prednisone, 13, 7, and 1

hour before the procedure and intravenous administration of 50 mg of diphenhydramine, with or without 25 mg of ephedrine, 1 hour before the infusion of RCM. Prednisone-diphenhydramine-ephedrine and prednisone-diphenhydramine prophylaxis have been shown to be equally efficacious.<sup>56–58</sup>

### *Hemostatic Agents (Protamine and Aprotinin)*

Protamine adverse reactions usually comprise 3 different types: systemic hypotension, anaphylactic and anaphylactoid reactions, and catastrophic pulmonary vasoconstriction. Anaphylactic reactions have been attributed to various mechanisms, including complement activation and protamine-specific IgE and IgG. Although protamine is administered intravenously to neutralize the anticoagulant effects of heparin in cardiopulmonary bypass and vascular surgical procedures, it is not a common cause of anaphylaxis during such surgical procedures.<sup>59</sup> Insulin-dependent diabetes mellitus with previous use of protamine-containing insulin preparations has been shown to be a risk factor.<sup>60</sup> Allergy to fish has not been conclusively shown to be associated.<sup>61,62</sup> Skin prick tests and specific IgE levels have not been demonstrated to be clinically useful in the diagnosis of hypersensitivity to protamine.<sup>63</sup> Aprotinin, a broad-spectrum serine protease inhibitor, has also been described as a cause of intraoperative anaphylaxis where aprotinin-specific IgE using the CAP FEIA method and positive skin test reactions have been demonstrated.<sup>64,65</sup>

### *Other Unusual Causes of Intraoperative Anaphylaxis*

Recent reports have implicated isosulphan blue dye used for sentinel lymph node biopsy in the evaluation of breast cancer as an additional cause of intraoperative anaphylaxis. These cases were diagnosed based on the close temporal relationship between administration and onset of symptoms. There was no immunologic verification or exclusion of other agents using skin tests or measurements of specific IgE,<sup>66,67</sup> except for 1 case series.<sup>68</sup> Anaphylaxis has also been attributed to chlorhexidine used during surgery, with specific IgE and positive skin test reactions demonstrated.<sup>69,70</sup> Neostigmine, an anticholinesterase drug commonly used in the reversal of nondepolarizing neuromuscular blockade, has been reported as a rare cause of anaphylaxis in the late intraoperative period. Positive SPT reactions have been demonstrated with 2.5- and 0.25-mg/mL solutions.<sup>71</sup>

### *Blood and Colloid Infusion Products*

Apart from transfusion reactions from blood and blood products, colloid infusion products may also cause anaphylaxis during surgery. In a multicenter prospective trial, 69 cases of nonallergic anaphylaxis have been observed among 200,906 infusions of colloid volume substitutes. The frequency of severe reactions (shock and cardiac or respiratory arrest) was 0.003% for plasma-protein solutions, 0.006% for hydroxyethyl starch, 0.008% for dextran, and 0.038% for gelatin solutions.<sup>72</sup> Although the exact pathophysiologic mechanisms of these reactions from colloid solutions remain unclear, gelatin-specific IgE and positive SPT and intradermal test

reactions have been demonstrated in some cases, suggesting an IgE-mediated mechanism.<sup>73,74</sup> Laxenaire et al,<sup>74</sup> in a large, prospective study, identified a history of drug allergy and male sex as independent risk factors for anaphylaxis to colloid plasma substitutes. Reliable prophylactic measures are not universally acceptable. Better purification of polygeline and pretreatment with histamine H<sub>1</sub> receptor and H<sub>2</sub> receptor antagonists have both substantially reduced the frequency of clinical reactions.<sup>75</sup>

Selective IgA deficiency is the most common form of primary immunodeficiency in the Western world and affects approximately 1 in 600 individuals. However, there is marked variability in the prevalence in different ethnic groups, with a lower frequency in the Japanese (1 in 18,000) and Chinese (1 in 4,000). Common variable immunodeficiency affects approximately 1 in 25,000 white people. A systemic reaction following transfusion of properly matched blood may occur from anaphylaxis attributable to IgE and IgG antibodies to IgA in some IgA-deficient recipients with selective IgA deficiency or common variable immunodeficiency.<sup>76,77</sup> Anti-IgA anaphylactic transfusion reactions are rare events, estimated to occur in 1 in 20,000 to 47,000 transfusions. The diagnosis of an anaphylactic transfusion reaction is established by showing an anti-IgA antibody in the patient's serum.<sup>78</sup> There is no consensus on whether patients should be routinely screened for anti-IgA antibodies, partly because there is no agreement on the level of antibodies that constitutes a risk of anaphylaxis to blood products.

### Mastocytosis

Mastocytosis is a group of rare disorders characterized by a pathologic increase in mast cells in tissues, including skin, bone, marrow, liver, spleen, and lymph nodes. General anesthesia may precipitate severe reactions, including systemic hypotension, nonallergic anaphylaxis, and coagulopathy, especially in patients with a history of allergies or previous adverse reactions to GA agents.<sup>79</sup> Preoperative and postoperative monitoring of serum tryptase levels and blood coagulation parameters; close communication among anesthesiologists, surgeons, and intensivists; and preoperative avoidance of  $\beta$ -adrenergic blockers and mast cell stabilization are important in preventing complications from intraoperative mast cell degranulation.<sup>80–83</sup>

### CONCLUSION

Anaphylaxis during surgical and interventional procedures may be difficult to evaluate because of the rapid, successive use of multiple drugs or diagnostic agents. The correct diagnosis of the putative agent causing anaphylaxis during surgical or interventional procedures depends on a combination of clinical history, skin testing, and measurement of serum tryptase and specific IgE levels using radioimmunoassay, RAST, or CAP FEIA methods. The timing of onset of anaphylaxis (preoperative, immediate intraoperative, late preoperative, postoperative) may help determine the putative drug. Skin tests made from dilutions of the parent drug (except for

penicillins, for which standardized commercial reagents are available) are useful in helping to select anesthetic agents that can be potentially tolerated. Apart from serum tryptase and specific IgE for succinylcholine, most of the other in vitro assays are not commercially available and are used on a research basis. The FAST assay seems promising in providing an alternative commercially available assay. Desensitization for selected antibiotics and premedication with histamine receptor agonists and corticosteroids for RCM may prevent recurrence of anaphylactic reactions to the respective agents.

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